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13. ABSTRACT *(Maximum 200 words)*

This case-control study examines breast cancer risk in relation to lifetime alcohol consumption. Subjects are 1,350 pre-and post-menopausal women, age 35-79, from Erie and Niagara counties in New York State, with incident, pathologically confirmed breast cancer. Most controls have been interviewed as part of another study that has just ended. A small number of additional controls will be interviewed in the next years of this study to control for secular trends. Controls are randomly selected and frequency matched to cases on age, race and county of residence. Subjects receive a computerized interview that focuses on in-depth lifetime alcohol consumption history. Potential confounding factors are also assessed. A specimen bank is used to store biological samples for future research of serum and urinary markers of hormones, hormone metabolites, vitamins, genetic polymorphisms and blood levels of antioxidants and oxidative stress. This study provides an important opportunity for an efficient examination of alcohol and other risk factors, particularly genetic variability, in relation to breast cancer risk, with potential for clarification of a significant public health problem. Since the inception of the study, 264 breast cancer cases and 1,816 controls have been interviewed and blood samples stored for 228 cases and 1,683 controls.

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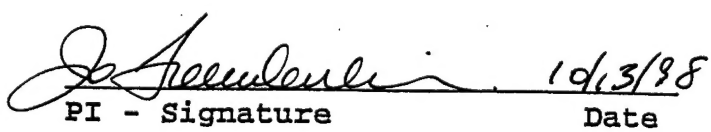

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TABLE OF CONTENTS

INTRODUCTION

This research is an epidemiologic investigation into the role of lifetime alcohol exposure in breast cancer etiology, research of considerable relevance to the issue of breast cancer prevention, providing insight on the role of a modifiable, and common exposure. It is being conducted in conjunction with two existing case-control studies as part of The Center for Clinical and Medical Epidemiology of Alcohol. These studies share the same protocol and control series.

In this case-control study, women age 35-79 from Erie and Niagara counties in western New York with incident, pathologically confirmed cases of breast cancer are being interviewed (215 premenopausal and 745 postmenopausal women). Controls are women interviewed as part of, previously funded, case-control studies. Controls are randomly selected, those under age 65 from lists provided by the New York State Department of Motor Vehicles, those age 65 and over from enrollment lists of the Health Care Finance Administration. Controls are frequency matched to cases on age, race, and county. Blood samples are stored in a biological specimen bank for future research.

The primary purpose of this study is to examine history of alcohol consumption from adolescence through adulthood as a risk factor for pre- and post-menopausal breast cancer in women. We will also examine the possible role of genetic factors, estrogen receptor status, histology, and use of estrogen replacement therapy among post-menopausal women in mediating the effect of alcohol on breast cancer risk.

While there is evidence that alcohol consumption may be involved in the etiology of breast cancer (1), results are not consistent and the mechanism of action is not well understood. A potential association between alcohol consumption and breast cancer risk was first suggested in the late 1970's (2). Since that time, numerous case-control and cohort studies have been conducted. A number of case-control studies have shown an increase in risk, generally on the order of 40-100% increase in breast cancer risk at the highest intake levels of alcohol (2-21) whereas others (22-28) have shown no evidence of increased risk. The most dramatic increase in risk was reported by Richardson et al. (13); consumption of more than 17 drinks per week was associated with more than three-fold increase in risk among women in Southern France. More moderate excess risk estimates were found in studies conducted in the United States (29, 30), Australia (14), Denmark (20), and New Zealand (31). An increase in risk of breast cancer with alcohol intake has been shown in most (32-36) but not all (37, 38) cohort studies. In a meta-analysis of the epidemiologic studies up to 1992, Longnecker (1) estimated that there was an increased risk of 11% associated with intake of one drink daily compared with abstention. In a combined analysis of six case-control studies, Howe et al. (39) estimated a risk of about 1.7 associated with the intake of ≥40g (about 3 drinks) of alcohol daily compared with non-drinkers. In a recent pooled analysis of six cohort studies, risk was 1.09 for each 10 grams per day of alcohol consumption. Risk increased approximately linearly with intake (40).

Several studies have examined whether the relationship between alcohol consumption and breast cancer risk differs among subgroups of women. There is some evidence that the

etiologic pathway for breast cancer may differ for premenopausal and postmenopausal women. While some studies suggest that alcohol increases pre-but not postmenopausal breast cancer risk (4, 10, 14, 32, 35), others suggest that excess risk only exists for postmenopausal women (41). Others found no effect of menopausal status on the relationship between alcohol consumption and breast cancer risk (42). Some studies would suggest that among postmenopausal women, only among those taking exogenous estrogen does alcohol affect risk. There is some evidence that the risk from alcohol exposure may differ according to whether or not a woman has a family history of breast cancer (33, 43). Two cohort studies, however, did not find the risk associated with alcohol consumption to differ depending on family history of the disease (35, 36). A case-control study in New York State reported that alcohol increased risk only of estrogen receptor positive and not estrogen receptor negative tumors. They did not see a difference in the association of alcohol with risk by cancer histology (45).

We recently found that genetic differences in alcohol metabolism may affect the association between alcohol consumption and breast cancer risk. We examined risk associated with a polymorphism in the gene for alcohol dehydrogenese (ADH_3). Using data and DNA collected from an earlier case-control study, we found that premenopausal women with the ADH_3^{1-1} genotype with alcohol intake above the median were at increased risk (OR 3.6,95% CI 1.5-8.8) compared to women who drank less and who had the ADH_3^{2-2} or ADH_3^{1-2} genotypes (44). The new study now underway will allow us to examine this potentially important relationship in a larger sample with better information regarding lifetime alcohol exposure.

There is also some evidence that the age at which a woman began drinking is of importance in breast cancer risk. Harvey and others (29) found that increased risk associated with alcohol intake was limited to women who began drinking before 30 years of age. In other studies of women in Wisconsin (3), Poland (46), and The Netherlands (4), there was evidence of increased risk for women who began drinking at earlier ages. In another study in Italy (5), risk was found to be unrelated to the age when drinking began and in a study in New York State, risk was inversely related to the age when drinking began (6). We examined exposure to alcohol in adolescence (16 years of age) and did not find any association with risk, except a weak indication of risk for early intake of hard liquor (42). Further research is needed regarding lifetime drinking and its effect on breast cancer. To our knowledge, studies have not examined age at first intoxication and other details of early drinking, nor has there been a detailed examination of drinking practices throughout life. Studies have generally examined recent consumption or age when drinking began only.

BODY OF REPORT

Task 1: Months 1-3: Obtain Institutional Review Board approval for the study at all area hospitals.

During this budget year, we completed task 1. We obtained approval from the Institutional Review Board of the one remaining hospital in the region. Eleven hospitals have now approved the protocol. One hospital has not approved the protocol. It is a small hospital which sees few cases. Another small hospital approved the protocol but asked that we wait to ascertain cases until a merger with a larger hospital was completed. The merger is nearing completion and we anticipate working with them soon. The exception is Sisters' Hospital, a major hospital, that would not allow us to use their patient population in spite of long negotiations and considerable effort on the part of both our group and the hospital Institutional Review Board. However, the practice of breast surgeons who see virtually all of the breast cancer patients at that hospital are cooperating fully with the study and allowing us to contact patients using their clinic records. Contact with physicians and health care professionals and other breast cancer advocates is ongoing to promote continued cooperation with the study.

Task 2: Months 1-3): Finalization of all arrangements for interviewing: training interviewers, necessary preparations of computer interview, printing of the paper section of the questionnaire, obtaining lists of potential controls from the Department of Motor Vehicles and the Health Care Finance Administration, purchase of all necessary supplies and equipment.

This task is complete and we are proceeding with interviews of breast cancer cases and controls. To date, we have interviewed 264 women with incident, primary, histologically confirmed breast cancer and 1,816 controls. Until now, controls have been interviewed as part of the funding of other case-control studies on the clinical and medical epidemiology of alcohol. Those studies utilized the same protocol and the same interview. However, those studies are now ending. An additional 150 controls will be interviewed during the remainder of this grant to ensure that there is no bias related to secular trends.

Training of interviews and supervision of interviewers regarding their administration of the interview is ongoing. We now have a group of interviewers who have been carefully trained and who have been working on this study for up to four years. We meet regularly with them to discuss any concerns and to continue to standardize procedures. We have approval from the Department of Motor Vehicles and from the Health Care Finance Administration to provide us with lists of potential controls and we receive periodic updates from those two sources.

Task 3: Months 4-45): interviewing of cases and controls: approximately 434 interviews in the remainder of yr 1, 579 in yr 2, 302 in yr 3 and 185 in yr 4. Interviewing for postmenopausal white women will conclude approximately at the end of month 27. Interview of 150 controls will be conducted in the period months 32-45. All other case interviews will be spread over the entire period.

As noted above, the interview of cases is continuing. We had originally anticipated that we would interview approximately 1,000 cases during the first two years of the study. In fact we have

interviewed 264. This delay is related to several factors. It took longer than expected to obtain Institutional Review Board (IRB) approval from area hospitals, mostly because of scheduling of IRB meetings by hospitals and some difficulties with restrictions in the consent form imposed by the Army. Case ascertainment began March, 1997 instead of the anticipated start date of December, 1996. There has been some additional delay in that we have determined, based on our experience and based on advice from clinicians, that it is advisable to wait two to four months after diagnosis before contacting patients for participation in the study. Even with this delay in contacting patients, we find that there are a significant number of patients who want to wait longer to be interviewed. Our case ascertainment is somewhat lower than we had predicted based on estimates provided by the New York State tumor registry. We are finding about 86% of the cases that we had expected based on their estimates. This difference is most likely related to the hospitals who have not participated in the study and to patients ascertained by the registry only by death certificate. Additionally, our participation rate is lower than anticipated. We are interviewing approximately 54% of the patients whom we ascertain. There are several reasons for the lack of participation. There are a few physicians who have not agreed to participate in the study in spite of several meetings and attempts to secure their cooperation. Additionally, our interview is relatively long. Some of the breast cancer patients are unwilling or unable to participate. We make every effort to provide means for case participation. We interview women in their homes, we provide taxi service to those who require that, and we arrange interviews for any time of the day and on weekends. These rates, while low, are comparable to those in our recently completed case-control study of myocardial infarction and are considerably higher than the participation rates for a case-control study of lung cancer. These rates appear to be as good as possible for a study of this kind in this region.

In order to determine to some extent bias related to lack of participation, we have collected a small amount of data on both participants and on those refusing to participate. At the time of the initial phone contact with the women, we ask several questions. To date, we have information entered on 131 women who completed the interview and 68 women whom we asked questions over the phone but who were not willing to be interviewed. In comparisons of these women, we find that there was no difference among those participating and those who did not in terms of amount that they currently drink, or whether they ever drank and decided to quit. There was also no difference between participants and non-participants in terms of whether they had ever had a mammogram. Those participating were somewhat better educated (13.8 compared to 12.4 years of school completed on average). The participants also reported eating, on average, one serving more of vegetables per week, and reported more physical activity. They were less likely to be a current smoker; there was, however, no difference in the two groups in whether they had ever smoked. These data provide some assurance that the two groups do not differ greatly with regard to alcohol consumption and screening behaviors. There may be some selection with regard to some other health practices such as diet, physical activity and smoking.

Based on our experience in the past year, we find it necessary to revise the Statement of Work. During years 3 and 4 we will interview 700 cases, making a total of 960 (approximately 215 premenopausal and 745 postmenopausal women). We will continue interviews of postmenopausal white women in years three and four. In addition, as noted above, we will interview 150 controls. With the smaller number of cases, we will still have adequate power to examine the primary hypotheses of the study. We will have reduced power, particularly for the premenopausal women and for some of the stratified analyses. However, we will have adequate

power for examination of the main effects and for stratification for the proposed analyses by alcohol dehydrogenase polymorphism. Power will be adequate for the examination of effect modification, particularly for the postmenopausal women. As noted in the original grant, there will be a relatively small number of incident cases for African American women. We will only be able to identify whether trends are the same as those for whites; we will not be able to test for interactions by race.

Task 4: Months 3-47: Ongoing data entry of the interview, maintenance of files from computer-assisted interview and entry of data from the sections of the interview completed by the participant.

All necessary arrangements for ongoing data entry of the interview, maintenance of files from the computer-assisted interview, and coding of data from the sections of the interview completed by hand by the participant are progressing in a timely fashion.

Task 5: Months 4-47: Maintenance of the biological specimen bank, processing of samples for immediate determinations and for storage, tracking of all samples, mapping of the freezer.

Procedures for the ongoing maintenance of the biological specimen bank are well underway. Means for tracking of samples and mapping of the freezer have been established and are progressing.

To ensure standardization of specimens collected, all blood is drawn at the same time of the day (7:00AM-9:00AM). For pre-menopausal women, blood drawings are scheduled for the luteal phase of the cycle to reduce, to the extent possible, variation in hormone levels related to the menstrual cycle. The time of the blood draw is recorded for assessment of any variation in blood markers related to the time of the draw. 1,683 control and 228 case blood samples have been processed for immediate determinations and for long term storage.

Two studies have been conducted this year as part of the quality control measures for the blood specimen bank. They are:

1) Reproducibility & Reliability of Serum β-Sitosterol and Campesterol in Premenopausal Women.

The aim of this study was to analyze the reproducibility and reliability of the serum phytosterols β-sitosterol and campesterol in premenopausal women. Phytosterols produce a wide spectrum of biological activities in animals and humans, and may reduce serum or plasma total cholesterol and low-density lipoproteim by inhibiting the absorption and synthesis of cholesterol (47, 52). There is recent evidence that phytosterols have anti-tumor properties in both animals and humans (47-51); they may also be related to risk of coronary heart disease (47, 53, 54). Subjects were premenopausal women in good health, non-smokers, with regular menstrual cycles. Samples were drawn and processed within the same time period and stored at -70°C. there were three subjects in the reproducibility study and seven in the reliability study. Each woman provided one blood sample (54ml) each month at the same numerical day of their menstrual cycle during six months. Samples were stored at -70°C. Serum β-sitosterol and campesterol were measured in both studies. Laboratory results are currently being analyzed.

2) Reliability of Oxidative Stress Indicators

The aim of this study is to assess the intra-individual variability and laboratory variability of biomarkers of oxidative stress and to investigate the reliability of three new markers of lipid peroxidation.

Subjects were 7 pre- and 5 post-menopausal women and 5 men, all non-smokers. Three specimens were collected from each participant with each blood draw taking place at the same time of the day at each of three visits: baseline one week and one month after baseline. For each individual, at each blood draw, one set of samples (each consisting of three subsets) were drawn, for a total of 27 samples per individuals by the end of the study. All laboratory determinations for each individual took place in the same run. At this time, laboratory analyses are underway.

In a previous reliability study we investigated the effect of transportation by car and delay in processing on the levels of several blood constituents in serum and plasma while controlling for other sources of variability. Fifty-one men between the ages of 26 and 50 were recruited for this study. Two sets of blood samples were collected from each patient. One set was processed immediately and the other was transported by car for one hour in order to reproduce the conditions of a home blood draw. The results from this study indicate that the transportation and delay in processing is a source of variability in the measurement of some biomarkers. These results are significant to epidemiological studies that collect blood during home visits and a central study center. A manuscript has been prepared for submission for publication.

Tasks 6-8: Months 25-48: Genetic analyses of samples: DNA extractions and determinations of genetic polymorphisms. Statistical analyses; preparation of variables from the interview and blood determination, all required analyses of the data for reports and presentations. Preparation of publications reports and presentation of the data.

Work on these objectives has not yet begun. As planned, DNA extraction will begin in the next funding year. Statistical analyses will begin when interviewing has been completed. In the next year, preliminary data sets will be assembled and necessary work begun on managing the data, identifying outliers and implementing procedures for cleaning the data.

CONCLUSIONS

We have just begun data collection for this grant, therefore there are no conclusions to report at this time.

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